Clinical Features, Management and Outcomes of Progressive Outer Retinal Necrosis (PORN) in Southern Thailand

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Objective: *To study the demographics, clinical features, treatment, and visual outcomes of progressive outer retinal necrosis (PORN) in a group of Thai patients.*
Material and Method: *All cases of AIDS with a clinical diagnosis of PORN in a major tertiary referral hospital in southern Thailand between January 2003 and June 2007 were retrospectively reviewed. Demographic data, clinical features, treatment regimens, and visual outcomes were analyzed.*
Results: *Seven patients (11 eyes) were studied. The mean age was 44.7 years. The median CD4 count was 12 cells/mm^3. A known history of cutaneous zoster was documented in 57% of cases. The median follow-up period was 17 weeks. Fifty-seven percent of the patients had bilateral disease. A majority of eyes (45.4%) had initial visual acuity of less than 20/50 to equal to or better than 20/200. About two-thirds of the eyes had anterior chamber cells. Vitritis and retinal lesions scattered throughout both posterior pole and peripheral retina were found in 72.7%. Either intravenous acyclovir in combination with intravitreal ganciclovir injections or intravenous aclyclovir alone was used for initial treatment. Retinal detachment occurred in 54.5%. Final visual acuity worsened (loss of 3 lines on the ETDRS chart or more) in 60%. Visual acuity was no light perception in 45.5% at the final recorded follow-up.*
Conclusion: *Demographics, clinical features and treatment outcomes of PORN in this group of Thai patients were comparable with studies from other countries. Visual prognosis is still poor with current treatment regimens.*

Keywords: *AIDS-Related opportunistic infections, Acquired immunodeficiency syndrome, Herpesvirus 3, Human, Retinal necrosis syndrome, Acute*

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Patients with acquired immunodeficiency syndrome (AIDS) are predisposed to several ocular posterior segment opportunistic infections such as those caused by members of the herpes virus family, *Toxoplasma gondii, Pneumocystis carinii, Candida* species, and bacteria[1].

Progressive outer retinal necrosis (PORN) is a clinically distinct necrotizing retinitis syndrome caused primarily by members of the herpes virus family. It is found almost exclusively in people with AIDS or other conditions causing immune-system compromise. It is an uncommon but potentially blinding necrotizing retinitis first reported in 1990 by Forster et al[2], who described this disease in two patients with AIDS and coined the term PORN.

Various studies have identified varicella zoster virus (VZV) as an etiologic agent of PORN[2-7]. Kashiwase et al also reported that herpes simplex virus type 1 (HSV-1) could be a causative agent as well[8].

PORN is characterized clinically as multifocal, discrete, opacified lesions beginning in the outer

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retinal layers of the periphery and/or posterior pole with few or no inflammatory cells in the anterior chamber or vitreous. There is no retinal vasculitis[9].

Most patients with PORN have a poor ophthalmologic prognosis because of an extremely rapid and progressive clinical course that may lead to no light perception in affected eyes within days or weeks, and currently available treatments with anti-viral agents have had only limited success[2,3,9]. Rhegmatogenous retinal detachment (RRD), which often occurs after the development of atrophic retinal holes within or at the margins of areas of inactive retinitis, also leads to poor visual outcomes[9].

The clinical features, disease course, and outcomes attributed to PORN have varied in previous reports, and there are no studies from Thailand. Thus, the authors decided to study a group of Thai patients as a different ethnic group and compare the results with other reports.

Material and Method

All cases of AIDS with a clinical diagnosis of PORN and a complete ophthalmic examination who were seen in Songklanagarind Hospital, the major tertiary referral center in southern Thailand, between January 2003 and June 2007 were reviewed. Eleven eyes of seven patients met the diagnostic criteria for PORN as described by Engstrom et al[9].

The following demographic and medical data were extracted from the medical records: patient age, sex, presenting CD4 lymphocyte count, any history of highly active antiretroviral therapy (HAART), including duration and history of extraocular herpes viral infection; clinical characteristics including laterality, initial visual acuity (VA), anterior chamber cells, posterior synechiae, keratic precipitate, vitreous inflammation and location of retinitis; and treatment regimens, clinical response, retinal detachment development, duration of follow-up and final visual acuity. Improvement of VA was defined as gaining at least 3 lines on the ETDRS chart while worsening was defined as loss of 3 lines or more. Data were summarized in term of case-by-case results.

Results

Seven patients (11 eyes) were studied. The demographic data of the seven patients are summarized in Table 1. There were six males and one female with a mean age of 44.7 years. The median CD4 count was 12 cells/mm^3 (range, 6-94 cells/mm^3). Antecedent cutaneous zoster was found in four patients (57.1%), three with herpes zoster ophthalmicus (HZO), and one with thoracic cutaneous herpes zoster. The date of active cutaneous zoster preceded the diagnosis of PORN by a median of 92.5 days (range 10-240 days). Three (42.9%) of the seven patients were being treated with HAART at the time PORN was diagnosed. The median duration of antiretroviral therapy was 30 days (range 15-60 days).

The ophthalmic findings at diagnosis are summarized in Table 2. The disease was unilateral at diagnosis in three patients (42.9%), while the remaining four (57.1%) presented with bilateral involvement at first presentation. No patient who presented with unilateral PORN became bilateral during the follow-up period.

The initial VAs were equal to or better than 20/50 in two eyes (18.2%), less than 20/50 to equal to or better than 20/200 in five eyes (45.4%), less than 20/200 to light perception in three eyes (27.3.%) and no light perception (NLP) in one eye (9.1%).

Anterior chamber cells were identified in seven eyes (63.6%): grade 1+ in two eyes (28.6%), grade 2+ in two eyes (28.6%), grade 3+ in two eyes (28.6%), and grade 4+ in one eye (14.2%). Posterior synechiae was present in one eye (9.1%). Keratic

Table 1. Medical and demographic data

Patient	Age (years)	Sex	CD4 count (cells/mm^3)	History of extraocular herpes infection	HAART
1	36	M	6	No	No
2	48	M	12	Yes, HZO	No
3	41	M	94	No	No
4	30	M	77	Yes, HZO	Yes
5	33	M	7	Yes, thoracic zoster	No
6	41	F	29	Yes, HZO	Yes
7	42	M	9	No	Yes

precipitates (KP) were observed in five eyes (45.4%), fine KP in four eyes and medium-sized KP in one eye. Vitritis was present in eight eyes (72.7%), with severity of 1+ in five eyes (62.5%), and 2+ in three eyes (37.5%).

The locations of retinal lesions were documented in all eyes. The lesions were present in both posterior pole and peripheral retina in eight eyes (72.7%), and in the peripheral retina alone in three eyes (27.3%).

Treatment regimens and clinical outcomes at the last recorded follow-up are summarized in Table 3. The median duration of follow-up of these patients

Table 2. Clinical characteristics of the seven patients at diagnosis

Patient	Eye	Presenting VA	A/C cells	Posterior synechiae	Keratic precipitate	Vitritis	Locations of retinal lesions
1	Right	20/160	4+	No	Yes (fine)	2+	P and Po
	Left	20/40	1+	No	No	2+	P
2	Right	FC 1’	3+	No	No	No	P and Po
	Left	NPL	No	No	No	1+	P and Po
3	Left	20/200	2+	Yes	Yes (fine)	1+	P and Po
4	Right	HM	2+	No	Yes (medium)	2+	P and Po
5	Left	20/125	3+	No	No	1+	P
6	Right	20/100	No	No	Yes (fine)	1+	P and Po
	Left	20/63	1+	No	Yes (fine)	1+	P and Po
7	Right	20/20	No	No	No	No	P
	Left	20/200	No	No	No	No	P and Po

A/C cells = anterior chamber cells, P = peripheral, Po = posterior pole, FC1’= finger count 1 foot, NLP = no light perception, HM = hand motion

Table 3. Summary of treatments and visual outcomes

Patient	Eye	Presenting VA	Initial treatment	Maintenance treatment	Disease response	RD	Time to detachment (weeks)	Final VA	Follow-up duration (weeks)
1	Right	20/160	IV ACV	Oral ACV	Quiescent	No		20/160	2
	Left	20/40				No		20/32	
2	Right	FC 1’	IV ACV	Oral ACV	Progress	Yes	4	NLP	17
	Left	NLP				No		NLP	
3	Left	20/200	IV GCV Intravitreal ACV	Oral ACV Intravitreal GCV	Quiescent	Yes	64	FC 1’	68
4	Right	HM	IV ACV Intravitreal GCV	Oral ACV Intravitreal GCV	Quiescent	No		20/50	24
5	Left	20/125	IV ACV Intravitreal GCV	Oral ACV	Quiescent	No		20/32	4
6	Right	20/100	IV ACV	Oral ACV	Progress	Yes	3	NLP	3
	Left	20/63				No		NLP	
7	Right	20/20	IV ACV	Oral ACV	Quiescent	Yes	24	HM	52
	Left	20/200		Intravitreal GCV*		Yes	1	NLP	

FC1’ = finger count 1 foot, NLP = no light perception, HM = hand motion
IV = intravenous, ACV = acyclovir, GCV = ganciclovir, RD = retinal detachment
* To both eyes

was 17 weeks (range 2-68 weeks). Two different treatment regimens were used as initial therapy. Intravenous acyclovir 10-15 mg/kg/day alone was used in four patients (57.1%) as initial therapy for a median duration of 14 days (range 7-14 days), while intravenous acyclovir 10-15 mg/kg/day combined with intravitreal ganciclovir injections (2mg/0.1ml) was used as initial therapy in three patients (42.9%).

Maintenance therapy was provided to all patients. There were three different treatment regimens used as maintenance therapy. Two patients (28.6%) received oral acyclovir 800 mg five times per day for six weeks, two patients (28.6%) received oral acyclovir 400 mg five times per day for six weeks, and three patients (42.8%) received oral acyclovir 800 mg five times per day for six weeks combined with intravitreal ganciclovir injections (2mg/0.1ml). A median of six injections were given per eye (range 2-8 injections). Following the initiation of treatment, the disease became quiescent in five patients (7 eyes, 63.6%) and progressed in two patients (4 eyes, 36.4%).

Retinal detachment occurred in six (54.55%) of 11 eyes (4 patients). One of those had a detachment at the time of diagnosis while the others became detached after the treatment was begun at a median of 4 weeks (range, 1-64 weeks). Only one eye (case 7) underwent surgical repair by pars plana vitrectomy, endolaser, and silicone oil injection, in which the retina had been successfully reattached at final follow-up, although VA could not be properly assessed (listed as 'hand motion') as the silicone oil had not yet been removed. The other five eyes did not have surgical repair of the RRDs because of the expectation of poor visual outcome.

At the last recorded follow-up visit, the VA had improved (a gain of 3 lines on the ETDRS chart or more) in two eyes (20%), remained unchanged in two eyes (20%) and worsened (loss of 3 lines on the ETDRS chart or more) in six eyes (60%) (1 eye with initial VA at NLP was not included). The final VA was equal to or better than 20/50 in three eyes (27.3%), less than 20/50 to equal to or better than 20/200 in one eyes (9.1%), less than 20/200 to light perception in two eyes (18.1%) and no light perception in five eyes (45.5%) (Fig. 1).

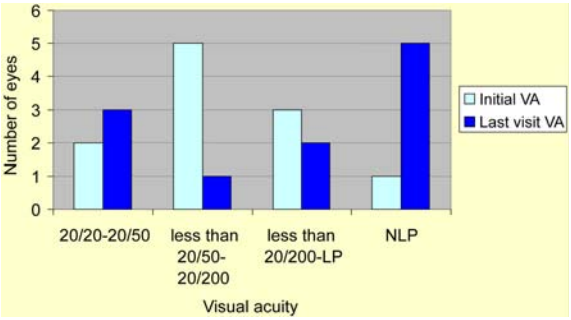
Discussion

Progressive outer retinal necrosis (PORN) is a morphological variant of necrotizing herpetic retinopathy as first described by Forster et al[2] in immunocompromised individuals. It is associated with minimal intraocular inflammation and has a rapidly progressive course. Early in its course, this condition is characterized by multiple deep retinal opacifications, giving the impression of an "outer retinitis". These lesions typically spare the perivascular retina. As the disease progresses, full thickness of the retina is involved forming necrotic, large retinal breaks leading to rhegmatogenous retinal detachment in the majority of affected eyes, contributing to the overall poor prognosis. The diagnosis of PORN is always clinical, based on a characteristic presentation.

PORN is frequently compared and contrasted with acute retinal necrosis (ARN), a necrotizing herpetic retinopathy and a distinct clinical entity that occurs in immunocompetent patients. ARN is characterized by the clinical trial of peripheral retinitis, vitritis, and retinal arteritis. In contrast to PORN, there is prominent vitreous and anterior chamber inflammatory reaction[10].

Varicella zoster virus (VZV) has been identified as the causative agent of PORN in several previous studies through various methods[2-7]. Forster et al[2] demonstrated virus particles consistent with a herpes virus from an electron microscopy retinal biopsy in one patient, while using polymerase chain reaction to reveal the herpes virus in another patient. Margolis et al[3] demonstrated VZV in vitreous and retinal cultures with electron microscopy and immunohistochemical analysis in three of five patients with PORN. In the present study, unfortunately, the authors did not have any microbiological data results to identify causative agents in the patients because the polymerase chain reaction technique for identifying organisms is not routinely performed in Songklanagarind Hospital.

Engstrom et al[9] reported that 67% of their patients had a cutaneous zoster infection prior to or



LP = light perception, NLP = no light perception

Fig. 1 Visual acuity (VA) at initial and last visits

coincident with PORN. Moorty et al[11] also found that 75% of patients in their study had previous or concurrent extraocular manifestations of VZV infection and their infections were not necessarily herpes zoster ophthalmicus. The same study also reported zoster meningitis and disseminated zoster viremia. Fifty-seven percent of the patients in the present study had a history of previous cutaneous zoster infection. Of these, 75% were HZO, the others thoracic cutaneous zoster, a finding comparable to other studies.

The various studies examining PORN have found that the most characteristic findings at diagnosis include multiple discrete areas of deep retinal opacification and no or minimal intraocular inflammation. Margolis et al[3] reported five patients with PORN and emphasized early posterior pole involvement as a feature, which differentiated PORN from ARN. However, a later report involving 38 patients[9] found that only one-third of all patients presented with posterior pole lesions. In the present study, 72.7% of patients presented with both posterior pole and peripheral lesions, and no patients presented with posterior pole lesions only.

The present study also found that anterior chamber and vitreous reaction were not prominent. Seven eyes had anterior chamber cells, of these 86% (6 eyes) had grade 1+ to 3+. Vitritis was found in 72.7% (8 eyes); of these, it was grade 1+ in five eyes (62.5%).

The quick control of PORN is important due to its rapidly destructive nature and the high likelihood of retinal detachment. Presently, there is no standard medical treatment regimen that has been agreed upon to treat PORN since the chorioretinitis responds inconsistently to antiviral agents.

Because VZV was identified as the causative agent of PORN in earlier studies, intravenous acyclovir was given, as this is an effective VZV treatment. However, intravenous acyclovir treatment has given poor results when used for PORN. Margolis et al[3] reported five patients with PORN, three of whom were treated with intravenous acyclovir. Despite this treatment, however, the disease continued to progress and the vision of all patients continued to decrease to NLP. Engstrom et al[9] described 38 PORN patients for whom acyclovir was the sole therapy in the majority, and although it seemed to reduce the disease activity it did not alter the final visual outcomes, as the final VA was NLP in 67% of the eyes within four weeks of diagnosis. PORN has also been found to recur following changes in medication delivery such as tapering or switching from intravenous to oral treatment[2-3].

In the above studies and others, following the poor results with acyclovir, other antiviral drugs such as foscarnet, ganciclovir, vidarabine, and combination regimens were attempted to improve treatment outcome. Moorthy et al[11] showed that treatment with intravenous ganciclovir, either alone or in combination with foscarnet, was associated with significantly better VA than with acyclovir alone. Around 90% of the acyclovir treated eyes had a final VA of NLP, while only 34% of the ganciclovir treated eyes, either alone or in combination with foscarnet had a final VA of NLP.

Pavesio et al[5] have suggested that intravitreal antiviral drugs may also be useful in the management of PORN because high levels of ganciclovir and foscarnet can be attained in the vitreous cavity and retina. Scott et al[14] reported on seven patients with PORN who were treated with intravenous ganciclovir and intravenous foscarnet combined with intravitreal ganciclovir injections, either alone or in combination with intravitreal foscarnet, and 45% of the eyes achieved a final VA of 20/80 or better and only 18% progressed to NLP.

In the present study, all patients were treated with intravenous acyclovir 10-15 mg/kg/day with a median duration of 14 days. In addition, four patients (5 eyes) also received intravitreal ganciclovir injections, with results that the vision was either maintained or improved in 40% of eyes. The final VA was NLP in 45.5% of all eyes after a median follow-up period of 17 weeks. Comparing the visual outcomes between the group which received the intravenous acyclovir alone with the group that received both intravenous acyclovir and intravitreal ganciclovir injections, the latter group had a slightly better final VA than the former group. Only one (20%) of five eyes progressed to NLP and two (40%)of five eyes achieved a final VA of 20/50 or better in the group which received both intravenous acyclovir and intravitreal ganciclovir injections after a median follow-up period of 38 weeks, results comparable with the earlier study noted of Scott et al.

However, comparing treatment outcomes between intravenous acyclovir and combined intravenous acyclovir with intravitreal ganciclovir injections was not the primary focus of the present study, and a randomized controlled trial is required to further elucidate the potential role of intravitreal antivirals in the treatment of PORN.

Rhegmatogenous retinal detachment (RRD) also contributes to poor visual outcomes in PORN cases and has occurred in about 70% of the eyes in prior studies[9,11]. In the present study, RRDs developed in

six of 11 eyes (54.5%) within a median period of four weeks of presentation. The slightly lower detachment rate in the present study may be due to the shorter follow-up period.

The present study had some limitations, most notably that it was a retrospective descriptive study with a small number of cases and also the diagnoses were based on clinical characteristics only. Microbiological results to identify causative organisms, which the authors did not obtain, would be essential data for a more firm and accurate diagnosis of PORN.

In conclusion, the present study reports the demographic data and clinical manifestations of a group of Thai patients with PORN, which were not significantly different from previous studies from other countries. The visual outcomes in the presented patients, treated with current treatment regimens, were still poor, and nearly half of the eyes progressed to NLP vision. Hence, The challenge remains to find a successful treatment regimen that works for all or most cases of PORN. A larger group of cases and prospective randomized controlled trial are required to determine the best treatment for patients with this disorder.

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อาการทางคลินิก วิธีการรักษา และผลการรักษาผู้ป่วยโรคติดเชื้อไวรัสจอตา progressive outer retinal necrosis (PORN) ในภาคใต้ของประเทศไทย

วันทนีย์ สิทธิวรากุล, นิพัฒน์ เอื้ออารี

วัตถุประสงค์*: เพื่อศึกษาลักษณะของผู้ป่วย อาการแสดงทางคลินิก วิธีการรักษาและผลการรักษาโรคติดเชื้อไวรัสจอตา PORN ในผู้ป่วยไทยกลุ่มหนึ่ง*

วัสดุและวิธีการ*: ศึกษาย้อนหลังโดยเก็บรวบรวมข้อมูลพื้นฐาน อาการแสดงทางคลินิก วิธีการรักษาและผลการรักษาของผู้ป่วยทุกรายที่ได้รับการวินิจฉัยเป็นโรคติดเชื้อไวรัสจอตา PORN ร่วมกับมีภาวะกลุ่มอาการภูมิคุ้มกันเสื่อมในโรงพยาบาลระดับตติยภูมิหลักในภาคใต้ ตั้งแต่เดือนมกราคม พ.ศ. 2546 ถึง มิถุนายน พ.ศ. 2550*

ผลการศึกษา*: พบผู้ป่วย 7 ราย (11 ตา) อายุเฉลี่ยขณะเกิดโรค 44.7 ปี ค่ามัธยฐานของจำนวนเม็ดเลือดขาวชนิด CD4 12 เซลล์/ลบ.มม. ผู้ป่วยร้อยละ 57 มีประวัติติดเชื้อไวรัสงูสวัดที่ผิวหนังนำมาก่อน ค่ามัธยฐานของระยะเวลาติดตามการรักษา 17 สัปดาห์ ผู้ป่วยร้อยละ 57 มีอาการแสดงของ PORN ในตาทั้ง 2 ข้างที่การตรวจครั้งแรกระดับสายตาแรกรับส่วนใหญ่ (ร้อยละ 45.4) อยู่ในช่วงน้อยกว่า 20/50 ถึง 20/200 การอักเสบในช่องหน้าลูกตาพบประมาณ 2 ใน 3 ของตาทั้งหมด พบการอักเสบของน้ำวุ้นตาและพบตำแหน่งการอักเสบแรกรับของรอยโรคบนจอตาเกิดขึ้นทั้งส่วนกลางและส่วนริมจอตาอย่างละร้อยละ 72.7 การรักษาเริ่มต้นประกอบด้วยการฉีดยา acyclovir เข้าทางหลอดเลือดดำร่วมกับการฉีดยา ganciclovir เข้าน้ำวุ้นตา หรือการฉีดยา acyclovir เข้าทางหลอดเลือดดำอย่างเดียว พบจอตาลอกทั้งสิ้นร้อยละ 54.5 ร้อยละ 60 มีระดับสายตาที่การติดตามการรักษาครั้งสุดท้ายแย่ลง (ระดับสายตาลดลงมากกว่าหรือเท่ากับ 3 แถวของแผ่นตรวจ ETDRS) และมีระดับสายตามองไม่เห็นแสงทั้งสิ้นร้อยละ 45.5 ที่การติดตามการรักษาครั้งสุดท้าย*

สรุป*: ข้อมูลพื้นฐานของผู้ป่วย อาการทางคลินิก และผลการรักษาผู้ป่วยโรคติดเชื้อไวรัสจอตา PORN ในผู้ป่วยไทยกลุ่มนี้มีลักษณะใกล้เคียงกันกับผลการศึกษาในเชื้อชาติอื่น การพยากรณ์การมองเห็นยังไม่ดีเมื่อให้การรักษาทางยาดังที่รายงาน*